ARIC Manuscript Proposal # 3071

PC Reviewed: 11/14/2017 Status: _____ Priority: 2
SC Reviewed: _________ Status: _____ Priority: ____

1.a. Full Title: Association of Fasting Glucose and Diabetes with Orthostatic Hypotension, Falls, and Syncope in the ARIC Study

b. Abbreviated Title (Length 26 characters): Orthostatic Hypotension and Cardiovascular Disease in ARIC

2. Writing Group:
   Writing group members: Stephen P Juraschek, Natalie Daya, A. Richey Sharrett, B. Gwen Windham, Gerardo Heiss, Elizabeth Selvin, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __x___ [please confirm with your initials electronically or in writing]

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3. Timeline: Data analysis to begin after approval of this manuscript proposal. First draft should be available March, 2018.
4. **Rationale:**

Orthostatic hypotension (OH) is an important risk factor for a number of outcomes including syncope, falls, cardiovascular disease, stroke, and death.\(^1\)\(^-\)\(^3\) OH is defined as a drop in systolic (>20 mm Hg) or diastolic blood pressure (>10 mm Hg) within 3 minutes of standing\(^4\) and is thought to reflect underlying autonomic dysfunction.\(^5\) In patients with diabetes, OH is thought to arise from underlying diabetic neuropathy.\(^5\) However, growing evidence suggests that vascular disease may also play an important role in the development of OH.\(^6\)\(^-\)\(^8\) The exact etiology of OH in diabetes remains unclear. Recently, the ACCORD trial demonstrated that tight glucose control was not associated with orthostatic hypotension.\(^9\)

The ARIC Study affords a unique opportunity to comprehensively examine the relationship between diabetes and OH as well as some of its major sequelae: falls and syncope.\(^10\) OH was assessed via high quality, standardized protocols during visit 1 and was derived using standard clinical definition (a decrease of at least 20 mmHg SBP or a decrease of at least 10 mmHg DBP when changing positions from supine to standing) in 681/13,191 (5.2%) of participants. Furthermore, covariates known to be associated with OH and cardiovascular disease were also assessed at baseline, affording an opportunity to rigorously address confounding. In addition, the ARIC study included rigorous assessment of diabetes and diabetes medication use. With regards to falls, we have demonstrated previously that CMS claims are highly specific (but relatively insensitive) for detecting falls in ARIC.\(^11\) We have also previously shown a strong association of OH with syncope.\(^10\)

In this proposal, we will examine (1) the cross-sectional association of blood glucose with OH in persons without diabetes, (2) association of diabetes with falls or syncope longitudinally, and (3) whether this association is partially mediated by OH.

5. **Main Hypothesis/Study Questions:**

Primary study questions:
1. Is blood glucose (visit 1) associated with orthostatic hypotension in participants with and those without a diagnosis of diabetes?
2. Is diagnosed diabetes (self-reported diagnosis or glucose-lowering medication use) cross-sectionally associated with orthostatic hypotension at visit 1?
3. Is diabetes status independently associated with incident falls or syncope over time?
4. Does OH mediate the relationship between diabetes and incident falls or syncope, i.e. does adjustment for OH attenuate the association after confirming that diabetes is associated with OH and that diabetes is associated with falls (we have shown previously that OH is associated with falls)?

Hypotheses:
1. Elevated (not low) blood glucose, i.e. above normal values, will be associated with high baseline prevalence of OH in participants without a diagnosis of diabetes and in adults with a diagnosis of diabetes.
2. Diabetes will be associated with orthostatic hypotension.
3. Both blood glucose and diabetes will be associated with incident falls or syncope.
4. Adjustment for OH will attenuate the relationship between blood glucose or diabetes and incident falls or syncope.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design: Cross-sectional study for Study Questions 1 & 2 (association of blood glucose or diabetes with OH). Prospective cohort study for Study Questions 3 & 4 (association of blood glucose or diabetes with falls or syncope).

Exclusions:
- No OH assessment at visit 1
- Missing a blood glucose
- Missing diabetes status information
- Missing covariates of interest
- Persons of ethnicity other than African American or white
- African-Americans from Washington Co or Minnesota

Note: We will include non-fasting blood glucose measures given the association of fasting hypoglycemia with syncope and the possibility that persons with presyncope symptoms when fasted, may be volitionally non-compliant with the “fasting” aspect of the protocol to avoid feeling ill.

Exposure assessment:

Blood glucose was measured in nearly all ARIC participants at visit 1. Participants were asked whether they had been diagnosed with diabetes. Participants were also asked about diabetes medication use in the previous two weeks.

We will examine the following 5 categories of BG without diabetes or diabetes:
(1) low-normal BG (fasting BG <80 or non-fasting BG <100 mg/dL),
(2) high-normal BG (fasting BG of 80-99 or non-fasting BG of 100-139 mg/dL),
(3) pre-diabetes (fasting BG of 100-125 or non-fasting BG of 140-199 mg/dL),
(4) undiagnosed diabetes (fasting BG ≥126 or non-fasting BG ≥200 mg/dL), or
(5) diabetes (self-reported diagnosis or current medication use).

Cross-sectional primary outcome: orthostatic hypotension
Systolic blood pressure and diastolic blood pressure were measured up to 5 times in supine and standing positions at baseline. Orthostatic hypotension will be defined as a dichotomous variable, using the traditional definition of a 20 mm Hg drop in systolic blood pressure or 10 mm Hg drop in diastolic blood pressure upon changing from a supine to standing position. The drops in SBP or DBP will be based on an average of up to 5 measurements. We will look at individual measurements, measurement patterns, and continuous changes in sensitivity analyses.

Longitudinal outcomes: fall or syncope

Falls or syncope will be defined at the first occurrence of any related hospitalization or claim for inpatient or outpatient services after the baseline visit. These outcomes were identified via two sources: 1) active surveillance of all hospitalizations for all ARIC participants; and 2) linkage to Centers for Medicare and Medicaid Services (CMS) claims data from 1991-2013. The ARIC Study obtains hospitalization information from annual telephone contact with study participants and through surveillance of hospitals in the study communities (inpatient hospitalization data currently available from January 1st, 1988, through December 31, 2015). In the original ARIC protocol, surveillance was primarily focused on coronary heart disease, stroke, and heart failure outcomes, but thereafter included other diagnostic codes for hospitalized events, including those attributed to fall, fracture, syncope, and motor vehicle accidents.

Participant data were also linked to CMS claims data using a finder file that included participants’ social security numbers, sex, and date of birth through a matching process described previously. These claims were available for eligible persons derived from two forms of coverage: (1) fee-for-service (FFS) or (2) managed care organizations. CMS data included inpatient and outpatient claims for participants enrolled in FFS continuously after reaching CMS Medicare eligibility and those with intermittent FFS enrollment during the period of observation. While no outpatient claims were available for cohort participants enrolled in managed care programs, inpatient claims were available on a selective basis from the year 2008 onward.

MedPar files were used to identify inpatient CMS records for hospital encounters related to falls, fractures, syncope, and motor vehicle accidents. Outpatient falls and motor vehicle accidents were identified using the Clinical Classification System (CCS) category 2603, E codes, which were based on International Classification of Diseases, 9th revision (ICD-9) external cause of injury codes. Falls were identified using the following ICD9 codes: E880.X-E888.X. Syncope was defined by code: 780.2.

Other variables of interest:
Models will be adjusted for age, sex, race-study center, body mass index, heart rate, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, total cholesterol, cholesterol lowering medications, hypertension, anti-hypertensive use in
the past 2 weeks, alcohol use, education, leisure activity, smoking status, and 8-hr fasting status.

Data analysis:
Our primary analyses will be as follows:

- Cross-sectional examination of baseline characteristics by blood glucose and diabetes status (Table 1).
  - Means, proportions
- Cross-sectional examination of the 5 blood glucose/diabetes categories above with orthostatic hypotension using logistic regression (Table 2).
  - Models will be adjusted for the following covariates assessed at visit 1: age, sex, race-study center, body mass index, heart rate, high density lipoprotein cholesterol, triglycerides, total cholesterol, cholesterol lowering medications, hypertension, anti-hypertensive use in the past 2 weeks, alcohol use, education, leisure activity, smoking status, and 8-hr fasting status.
  - Figure 1 A-C: restricted cubic spline of OH (OR from logistic regression) for continuous blood glucose overall and in strata of no diabetes or diabetes based on self-report of medication use; 4 knots will be selected via Harrell’s method
- Association of BG categories with new falls or syncope via Cox proportional hazard models (Table 3)
  - Base model will be adjusted for the following covariates assessed at visit 1: age, sex, race-study center, body mass index, heart rate, high density lipoprotein cholesterol, triglycerides, total cholesterol, cholesterol lowering medications, hypertension, anti-hypertensive use in the past 2 weeks, alcohol use, education, leisure activity, smoking status, and 8-hr fasting status.
  - Figure 2 A-F: fully adjusted restricted cubic splines (4 knots, Harrell’s method) of continuous blood glucose (overall and in strata of diabetes) with hazard of fall or syncope (no OH adjustment)
- Mediation analysis (Table 4)
  - We have previously shown OH is associated with falls. However, this analysis is contingent on demonstrating that BG categories are associated with OH and diabetes is associated with new falls or syncope. Assuming we demonstrate the above in the analyses described prior we will proceed as follows.
  - Using Cox models adjusted for the covariates above, we will additionally adjust for OH assessed at visit 1, determine the independent relationship between BG categories and new falls or syncope
  - We will also examine this relationship in strata of OH and examine interaction terms between BG categories and OH assessed at visit 1 for new falls and syncpe
Sensitivity analyses will look at individual measurements, patterns of OH presentation (early vs late), and continuous changes in SBP per 5 mmHg or DBP per 5 mmHg.

- Models will be adjusted for the following covariates assessed at visit 1: age, sex, race-study center, body mass index, heart rate, high density lipoprotein cholesterol, triglycerides, total cholesterol, cholesterol lowering medications, hypertension, anti-hypertensive use in the past 2 weeks, alcohol use, education, leisure activity, smoking status, and 8-hr fasting status.

Limitations:
- Fewer participants have both diabetes and OH, which may affect power
- Claims-based events are subject to under-ascertainment
- OH data not available on all participants or after 3 minutes in participants
- Residual confounding is always a concern with observational studies.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X___ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? ____ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?  ____ Yes _x__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ____ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscce.unc.edu/ARIC/search.php

  ____x____ Yes  _______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?


11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __x__ Yes _____ No

11.b. If yes, is the proposal
   ___ A. primarily the result of an ancillary study (list number* __________)
   ___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at http://www.cscce.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscce.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript __x__ Yes _____ No.
References


